

Gastrointestinal tumors of the small bowel: prognostic roles of tumor stage and inflammatory markers

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ABSTRACT

Aims: Small bowel tumors are a heterogeneous group of malignancies, including gastrointestinal stromal tumors (GISTs), adenocarcinomas, neuroendocrine tumors (NETs), and myofibroblastic tumors, each with distinct prognostic implications. While tumor stage is a well-established prognostic factor, patient survival outcomes and systemic inflammatory markers also play a crucial role in disease progression. This study evaluates these factors comprehensively to enhance prognostic assessment in small bowel malignancies.

Methods: This retrospective study analyzed 25 patients diagnosed with small bowel tumors, including various histological subtypes. The prognostic significance of tumor stage (T and N classification), systemic inflammatory markers (neutrophil-to-lymphocyte ratio [NLR], platelet-to-lymphocyte ratio [PLR], albumin, and C-reactive protein [CRP]), and overall survival was assessed. Kaplan-Meier survival analysis was conducted to evaluate the association between tumor stage, inflammatory markers, and patient outcomes. Statistical analyses included independent sample t-tests, Mann-Whitney U tests, and Chi-square tests.

Results: The median age of the cohort was 63 years (range: 47–81). The most common histological subtype was GIST (52%), followed by adenocarcinoma (24%), NET (20%), and myofibroblastic tumors (4%). Kaplan-Meier survival analysis revealed a significant association between tumor stage and patient survival ($p=0.036$), with advanced-stage tumors (T3–T4) demonstrating significantly lower survival rates compared to early-stage tumors (T2). Lymph node involvement (N stage) was also a significant predictor of reduced survival ($p=0.013$). Although inflammatory markers such as NLR, PLR, albumin, and CRP were assessed, they did not show statistically significant associations with survival outcomes ($p>0.05$).

Conclusion: This study highlights the importance of evaluating both tumor stage and patient survival when determining prognosis in small bowel tumors. The Kaplan-Meier analysis underscores the strong prognostic impact of tumor staging and lymph node involvement on survival outcomes. Although systemic inflammatory markers did not show significant prognostic value in this cohort, their role in risk stratification warrants further investigation in larger studies. These findings contribute to a broader understanding of small bowel tumor prognosis beyond staging alone, supporting the need for a multidimensional approach in clinical assessment and treatment planning.

Keywords: Gastrointestinal stromal tumors (GISTs), inflammatory markers, tumor stage, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), survival analysis, gastrointestinal tumors, prognostic factors

INTRODUCTION

Small bowel tumors are rare but clinically significant neoplasms that represent a diverse spectrum of histological subtypes, including gastrointestinal stromal tumors (GISTs), adenocarcinomas, neuroendocrine tumors (NETs), and myofibroblastic tumors.^{1,2} These tumors, though uncommon compared to those arising in other parts of the gastrointestinal (GI) tract, pose significant diagnostic and therapeutic challenges due to their nonspecific symptoms and delayed diagnosis.³ Each histological subtype exhibits unique biological behaviors, prognostic implications, and therapeutic considerations.

GISTs are the most common mesenchymal neoplasms of the GI tract and are typically characterized by activating mutations in KIT or PDGFRA.¹ These mutations make GISTs amenable to targeted therapy with tyrosine kinase inhibitors, such as imatinib, which has significantly improved outcomes in these patients. Adenocarcinomas, in contrast, are epithelial tumors often presenting at advanced stages due to their insidious onset, leading to poor survival outcomes despite surgical and chemotherapeutic advancements.² NETs of the small bowel arise from enteroendocrine cells and frequently present with distinct clinical syndromes, such as carcinoid

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syndrome, necessitating a multidisciplinary approach for optimal management.^{3,4} Myofibroblastic tumors, while rare, contribute to the heterogeneity of small bowel tumors and are often associated with inflammatory processes, further complicating their diagnosis and treatment.⁵

Prognosis in small bowel tumors is influenced by several factors, including tumor stage, histological subtype, and systemic inflammatory response.^{6,7} Tumor stage, particularly the presence of lymph node or distant metastases, is a well-established prognostic factor in GI cancers, with advanced-stage tumors demonstrating significantly worse survival.^{8,9} Histological subtypes also play a crucial role in determining prognosis and response to treatment. For instance, GISTs respond favorably to targeted therapies, while adenocarcinomas often require aggressive multimodal treatment with limited success.¹⁰

In recent years, systemic inflammatory markers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), have emerged as potential prognostic indicators in various cancers, including GI tumors.^{11,12} These markers are thought to reflect the interaction between the tumor and host immune response, as well as systemic inflammation, which can promote tumor progression. Additionally, albumin levels and C-reactive protein (CRP) have been explored as markers of nutritional and inflammatory status, with low albumin and elevated CRP often associated with worse survival in cancer patients.^{13,14}

While previous studies have evaluated these markers individually, few have analyzed their combined prognostic significance across multiple histological subtypes of small bowel tumors. Moreover, given the rarity of these tumors, data on their prognostic factors remain limited, and most studies have focused primarily on GISTs, leaving other subtypes underrepresented in the literature.¹⁵

Small bowel tumors represent a heterogeneous group of malignancies, including GISTs, adenocarcinomas, NETs, and myofibroblastic tumors, each with distinct biological behavior and prognostic implications. While GISTs are the most well-known mesenchymal neoplasms of the GI tract, other histological subtypes also significantly impact disease progression and patient outcomes. This study evaluates the prognostic significance of tumor stage, overall patient survival, histological subtypes, and systemic inflammatory markers, such as NLR, PLR, albumin, and CRP, across multiple small bowel tumor subtypes. By adopting a comprehensive approach, this research aims to provide deeper insights into the factors influencing survival beyond tumor staging alone. Furthermore, the findings contribute to the growing body of evidence supporting the integration of inflammatory markers into clinical practice for improved risk stratification and personalized treatment planning in small bowel malignancies.

METHODS

This study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Date: 01/09/2023, Decision No: 771/01/2021). All procedures were

carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The retrospective data of 25 patients diagnosed with small bowel tumors, including GISTs, adenocarcinomas, NETs, and myofibroblastic tumors, were analyzed. The ages, genders, histological subtypes, and clinical parameters of the included patients were evaluated. Neutrophil, lymphocyte, and platelet counts, as well as the NLR, PLR, albumin levels and CRP levels, are recorded. The normal reference ranges for the laboratory parameters were as follows: neutrophils ($2.5-10 \times 10^9/L$), lymphocytes ($1.0-3.0 \times 10^9/L$), platelets ($150-450 \times 10^3/\mu L$), albumin (3.5–5.0 g/dl), and CRP (<5 mg/L). Additionally, the tumor stages (T and N stages), tumor locations, and clinical presentations of the patients were analyzed. Computed tomography (CT) imaging findings were also reviewed. Follow-up times and survival statuses were calculated using the Kaplan-Meier method. Statistical analyses were performed using independent Sample t-tests, Mann-Whitney U tests, and Chi-square tests. $p < 0.05$ was considered statistically significant.

Statistical Analysis

The descriptive statistics of the data are presented as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of the variables was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables with a normal (Gaussian) distribution, such as age, the NLR, and the PLR, are reported as mean $\pm$ standard deviation, while variables with non-normal distribution, such as lymphocyte counts and CRP, were reported as median and interquartile range (IQR). For the analysis of quantitative independent data, independent sample t-tests and Mann-Whitney U tests were used. For the analysis of qualitative independent data, the Chi-square test was used, and Fisher's exact test was applied when the Chi-square test assumptions were not met. The Kaplan-Meier method was used for a survival analysis. All analyses were performed using SPSS version 28.0.

RESULTS

This study analyzed the clinical and demographic characteristics of 25 patients with GI tumors to evaluate the prognostic significance of various parameters, including age, gender, histological subtypes, inflammatory markers, and tumor stage. The results are summarized as follows:

Patient Demographics

The median age of the cohort was 63 years (range: 47–81 years), with a mean age of 62.7 ± 9.1 years. Of the 25 patients, 14 (56%) were male, and 11 (44%) were female. The statistical analysis revealed no significant association between age, gender, and survival outcomes ($p > 0.05$).

Histological Subtypes

The cohort included patients with GISTs (52%, $n=13$), adenocarcinomas (24%, $n=6$), NETs (20%, $n=5$), and myofibroblastic tumors (4%, $n=1$). Histological subtype was not significantly associated with survival outcomes ($p=0.546$) (Table 1).

		Min-Max	Medyan	Mean±SD/n %
Age		47.0-81.0	63.0	62.7±9.1
Sex	Female			11/44.0%
	Male			14/56.0%
Histoloji	Adenocarsinom			6/24.0%
	GIST			13/52.0%
	Myofibroblastik tumor			1/4.0%
	NET			5/20.0%
Neutrophil		2810.0-24500.0	8140.0	9216.4±5142.2
Lymphocyte		700.0-4100.0	1180.0	1595.6±863.0
Platelet (x10 ³)		131.0-399.0	260.0	265.5±73.9
NLR		1.2-35.0	5.7	7.6±7.1
PLR		80.2-500.0	180.5	201.3±100.9
Albumin		2.0-4.5	3.3	3.3±0.7
CRP		0.2-30.0	4.4	6.5±6.9
T stage	II			11/44.0%
	III			7/28.0%
	IV			7/28.0%
N stage	0			16/64.0%
	I			6/24.0%
	II			3/12.0%
Presentation	Chron			2/8.0%
	Hematochezia			1/4.0%
	Incidental			1/4.0%
	Ischemia			3/12.0%
	Abdominal pain			4/16.0%
	Melena			5/20.0%
	Obstruction			6/24.0%
	Perforation			2/8.0%
	Jaundice			1/4.0%
Tumor area	Duodenum			1/4.0%
	İleum			12/48.0%
	Jejunum			12/48.0%
CT screening	Intramural hematoma			1/4.0%
	Tumor			15/60.0%
	Tumor+perforation			1/4.0%
	Mezenter ischemia			2/8.0%
	Obstruction			5/20.0%
	Perforation			1/4.0%

GIST: Gastrointestinal stromal tumor, NET: Neuroendocrine tumor, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, CT: Computed tomography, Min: Minimum, Max: Maximum, SD: Standard deviation

Inflammatory Markers

The mean NLR was 7.6±7.1, and the mean PLR was 201.3±100.9. While both the NLR and PLR tended to be elevated in patients with advanced-stage tumors, these differences were not statistically significant in relation to survival outcomes (NLR: $p=0.352$; PLR: $p=0.106$) (**Table 1**).

Albumin and CRP

Albumin and CRP levels were analyzed. The mean albumin level was 3.3±0.7 g/dl, and the mean CRP level was 6.5±6.9 mg/L. Neither the albumin nor CRP levels showed significant associations with survival outcomes (albumin: $p=0.358$; CRP: $p=0.956$) (**Table 1**).

Tumor Staging (T and N Stages)

Tumor staging revealed that 44% of the patients ($n=11$) were classified as T stage II, 28% ($n=7$) were classified as T stage III, and 28% ($n=7$) were classified as T stage IV. The Kaplan-Meier survival analysis demonstrated that tumor stage significantly influenced survival outcomes, with the patients in T stage II

showing a cumulative survival time of 123.2 months compared to 56.2 months for in the patients T stages III-IV ($p=0.036$).

For N stage, 64% of the patients ($n=16$) had no lymph node involvement (N0), while 24% ($n=6$) were classified as N1, and 12% ($n=3$) were classified as N2. The patients with N0 had significantly better survival outcomes than with N1 or N2 ($p=0.013$) (**Table 2**).

Tumor Location

Tumor location was categorized as the duodenum (4%, $n=1$), ileum (48%, $n=12$), and jejunum (48%, $n=12$). The statistical analysis showed no significant differences in survival outcomes based on tumor location ($p=0.821$) (**Table 1**).

Survival Outcomes

By the end of the study, 72% ($n=18$) of the patients were still alive, while 28% ($n=7$) were deceased. The median follow-up time was 34.9 months (range: 0.1–133.9 months), with a mean follow-up time of 53.0±45.0 months (**Table 3,4**).

Table 2. Comparative analysis of clinical and demographic characteristics in patients with T stage II and T stage III-IV gastrointestinal tumors

		T stage II		T stage III- IV		P
		Mean±SD/n-%	Medyan	Mean±SD/n-%	Medyan	
Age		65.7±9.8	65.0	60.3±7.9	62.0	0.139 ^t
Sex	Female	4/36.4%		7/50.0%		0.495 ^{X²}
	Male	7/63.6%		7/50.0%		
Histologia						
Adenocarsinom		2/18.2%		4/28.6%		0.546 ^{X²}
GIST		7/63.6%		6/42.9%		0.302 ^{X²}
Myofibroblastik tumor		1/9.1%		0/0.0%		0.440 ^{X²}
NET		1/9.1%		4/28.6%		0.227 ^{X²}
Neutrophil		9466.4±3400.4	8710.0	9020.0±6310.9	6025.0	0.352 ^m
Lymphocyte		1895.5±979.5	1500.0	1360.0±707.8	1070.0	0.055 ^m
Platelet (x10 ³)		275.9±81.1	295.0	257.3±69.7	251.5	0.543 ^t
NLR		5.7±2.6	6.1	9.0±9.1	5.3	0.956 ^m
PLR		164.4±62.7	152.0	230.3±117.1	215.3	0.106 ^t
Albumin		3.1±0.7	2.9	3.4±0.8	3.6	0.358 ^t
CRP		5.7±4.5	5.9	7.1±8.4	4.0	0.956 ^m
N stage	0	10/90.9%		6/42.9%		0.013 ^{X²}
	I	1/9.1%		5/35.7%		
	II	0/0.0%		3/21.4%		
Location	Duedonum	0/0.0%		1/7.1%		1.000 ^{X²}
	Ileum	5/45.5%		7/50.0%		0.821 ^{X²}
	Jejenum	6/54.5%		6/42.9%		0.561 ^{X²}
Ex	(-)	10/90.9%		8/57.1%		0.062 ^{X²}
	(+)	1/9.1%		6/42.9%		
Following time		74.7±47.2	87.7	36.0±36.3	27.0	0.055 ^m

GIST: Gastrointestinal stromal tumor, NET: Neuroendocrine tumor, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-reactive protein, CT: Computed tomography, SD: Standard deviation, t: Independent sample t test, m: Mann-Whitney U test, X²: Ki-kare test (Fischer test)

Table 3. Survival status and follow-up duration of patients

		Min-Max	Medyan	Mean±SD/n %
Ex	(-)			18/72.0%
	(+)			7/28.0%
Following time		0.1-133.9	34.9	53.0±45.0

Min: Minimum, Max: Maximum, SD: Standard deviation

Table 4. Cumulative survival time by tumor stage in patients with gastrointestinal tumors

		Cumulative survival time (mounth)	% 95 GA	p
T grade	II	123.2	103.6-142.8	0.036
	III-IV	56.2	30.5-81.9	
Total		94.2	70.0-118.4	

Kaplan Meier (log rank)

Table 3 provides a summary of survival distributions, highlighting the percentage of patients with favorable versus poor outcomes. These data allow for a better understanding of survival trends within the cohort, despite the limitations posed by the sample size. **Table 2** presents detailed analyses of prognostic factors, including tumor stage, histological subtypes, and systemic inflammatory markers such as NLR and PLR. While some markers did not reach statistical significance due to the small cohort, the trends observed align with findings in larger studies and warrant further investigation.

Kaplan-Meier Analysis Section

To provide a comprehensive prognostic evaluation, we assessed not only tumor stage but also overall patient survival using Kaplan-Meier survival analysis. As shown in **Table 4**, survival outcomes significantly varied based on tumor stage, with patients diagnosed at T stage II demonstrating markedly improved survival compared to those with more

advanced-stage disease (p=0.036). Furthermore, lymph node involvement (N stage) was strongly associated with reduced survival, reinforcing its prognostic importance (p=0.013).

DISCUSSION

GISTs represent a unique subset of GI neoplasms, distinguished primarily by the presence at the KIT mutation, which has profound implications for treatment and prognosis.¹⁶ In this study, we aimed to evaluate the clinical characteristics, prognostic markers, and survival outcomes of patients with GI tumors, focusing on the impact of tumor stage, inflammatory indices, and histological subtypes on survival. Our findings contribute to the growing body of literature suggesting that both tumor biology and systemic inflammatory responses are significant determinants of patient outcomes.¹⁷

One of the key findings of our analysis is the strong association between tumor stage and survival outcomes. Patients with T stage II tumors demonstrated significantly longer survival than with stage III or IV tumors (p=0.036). This result is consistent with that of previous studies, emphasizing the critical role of early-stage diagnosis in improving the long-term prognosis of GISTs and other GI tumors.¹⁸ Early-stage tumors are often localized, making complete surgical resection more feasible, whereas advanced-stage tumors frequently exhibit metastasis or lymph node involvement, complicating surgical interventions and overall management.¹⁹

Another important aspect of our study is the evaluation of inflammatory markers, including the NLR and PLR. Elevated NLRs and PLRs have been shown to correlate with worse survival outcomes in a variety of cancers, including GI malignancies.²⁰ In our study, although the NLR and PLR were

elevated in more advanced stages, the differences between the stages were not statistically significant. This may be due to the relatively small sample size, limiting the statistical power to detect subtle differences. However, the trend observed is consistent with the hypothesis that systemic inflammation plays a role in cancer progression and may be associated with poorer outcomes.

The role of systemic inflammation in cancer progression is well established. Elevated NLRs and PLRs are indicative of a heightened inflammatory state, which may promote tumor growth and metastasis by creating a favorable microenvironment for cancer cells.²¹ Although our study did not find statistically significant differences in the NLR and PLR between stages, the potential prognostic value of these markers should not be overlooked. Larger studies are warranted to further explore the utility of these markers in clinical practice.

Albumin, a well-known marker of nutritional status and systemic inflammation, was another variable of interest in our study. Low albumin levels are commonly associated with poor prognosis in cancer patients due to their correlation with malnutrition and systemic inflammation.²² Our results show no significant differences in albumin levels between early and advanced stages, which may again be due to the small sample size. However, low albumin levels were more frequently observed in patients with advanced disease, aligning with the literature that suggests a relationship between hypoalbuminemia and worse clinical outcomes.

CRP, another inflammatory marker, was also assessed in our study. Elevated CRP levels have been linked to poor outcomes in various cancers, including GI tumors.²³ Although CRP levels were higher in patients with more advanced disease in our cohort, these differences were not statistically significant. Nonetheless, CRP remains a valuable marker in clinical practice, particularly in assessing systemic inflammation and guiding treatment decisions.

Histological subtype is another critical factor influencing the prognosis of GI tumors. GISTs, which made up the majority of cases in our study, are generally more responsive to targeted therapies such as tyrosine kinase inhibitors than adenocarcinomas or NETs.²⁴ This is largely due to the presence of a KIT mutation, which can be specifically targeted with drugs such as imatinib.²⁵ In our study, patients with GISTs had generally better survival than those with adenocarcinoma or NETs, although the differences were not statistically significant. This observation is consistent with other reports suggesting that the molecular characteristics of GISTs confer a more favorable prognosis when treated appropriately.

Our study also examined the impact of lymph node involvement (N stage) on survival. Patients without lymph node metastasis (N0) had significantly better survival outcomes than those with lymph node involvement (N1 or N2) ($p=0.013$). This finding aligns with that of previous research indicating that lymph node involvement is a strong negative prognostic factor of GI cancers.²⁶ The presence of metastatic lymph nodes often reflects more aggressive disease

and may reduce the effectiveness of surgical resection, leading to poorer outcomes.^{27,28}

Our findings highlight the necessity of evaluating prognosis beyond tumor stage alone. The significant differences in survival outcomes observed between early and advanced tumor stages indicate that overall survival should be a key consideration when assessing disease prognosis. The Kaplan-Meier survival analysis in our study confirms that lymph node involvement and advanced T stage correlate with poorer patient outcomes, a finding consistent with previous research on GI malignancies. These results underscore the importance of integrating both tumor stage and patient survival data when determining prognostic indicators for small bowel tumors.

Limitations

Despite the valuable insights provided by this study, several limitations should be noted. First, the retrospective nature of the study introduces potential biases, including selection bias and incomplete data. Additionally, the relatively small sample size limits the generalizability of the findings and reduces the statistical power to detect differences in some variables, particularly inflammatory markers such as the NLR, the PLR, albumin, and CRP. Future studies with larger cohorts and prospective designs are needed to validate these findings and explore the potential for integrating inflammatory markers into routine prognostic assessments for GI tumors.

CONCLUSION

Our study highlights the critical role of tumor stage in determining survival outcomes in patients with GI tumors. Early detection and appropriate staging are essential for improving prognosis. While systemic inflammatory markers such as the NLR, the PLR, and CRP were not found to be significantly associated with survival in this cohort, their potential utility as prognostic tools warrants further investigation. Targeted therapies, particularly for GISTs, continue to play a key role in improving outcomes, and the presence of lymph node involvement remains a significant negative prognostic factor. Future research should aim to refine the prognostic models for GI tumors, incorporating both traditional factors such as tumor stage and emerging biomarkers of systemic inflammation.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Haydarpaşa Numune Training and Research Hospital (Date: 01/09/2023, Decision No: 771/01/2021).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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